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AGE-RELATED CHANGES IN MOTOR ABILITY AND MOTOR LEARNING IN TRIPLE TRANSGENIC (3×TG-AD) AND CONTROL (B6129SF1/J) MICE ON THE ACCELERATING ROTAROD

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ABSTRACT

Mouse models of Alzheimer's disease (AD) show both cognitive and neuromotor impairments. We measured motor ability and motor learning of male and female triple transgenic (3×Tg-AD) and control (B6129SF1/J) mice on the accelerating Rotarod in a cross-sectional design at 2, 6, 9, 12, and 15 months of age. At all ages except for 2 months, transgenic mice performed better and had a steeper motor learning curve than controls. Female mice showed better motor performance than males, while males had a steeper learning curve than females. Age did not have a significant main effect on Rotarod performance. However, age and genotype showed an interaction, where the performance of 3×Tg-AD mice peaked at 6 months of age and decreased as age increased. The performance of controls was below that of 3×Tg-AD mice at each age. Behavioural differences seen in the 3×Tg-AD mice may help us to understand the development of neuromotor dysfunction in AD.

Keywords: Alzheimer's disease, Alzheimer models, Amyloid beta, motor ability, motor learning, Rotarod, tau, transgenic, 3×Tg-AD mice

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in humans (Alzheimer's Association 2011). Currently, over 26 million individuals have AD worldwide, and this number is expected to triple by 2050 (Brookmeyer et al. 2007). In Canada, AD accounts for more than 50% of dementia diagnoses, and there are over 100 thousand

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new cases of dementia per year, which is predicted to double by 2030 (Alzheimer Society of Canada 2010). In the same time frame, Nova Scotia's 3,200 new cases of AD per year are projected to double, and more than 2% of Nova Scotia's population will suffer from dementia (Smetanin et al. 2009). Alzheimer's is a neurodegenerative disease, leading to an early death (Mayeux 2010). After onset, those with AD experience short-term memory loss and, as the disease advances, they develop symptoms of confusion, long-term memory loss, and impairments in language and motor function (Castellani et al. 2010, Budson & Solomon 2012).

Two principal markers of AD have been identified in the brain: extracellular deposits of amyloid beta (Aβ) protein and intracellular neurofibrillary tangles of tau proteins (Hardy & Allsop 1991, Huang & Mucke 2012). However, the link between Aβ and tau proteins in the development of AD is not understood. Immunizations which reduce Aβ accumulation had no affect on AD symptom development; therefore, there must be other factors at work (Holmes et al. 2008, Robakis 2011). At present, there is no cure for AD and few treatments have had success. To study AD, it is useful to turn to simple animal models. While no model accurately represents AD pathology as a whole, the changes in Aβ neuropathology with age have been modeled in mice (Gilley et al. 2011). The present study investigates the triple transgenic mouse model of AD (3×Tg-AD), which has become an important tool in the development of pharmacological and behavioural therapy against AD (García-Mesa et al. 2011).

The 3×Tg-AD mouse model was created by microinjection of APP_{Swe} and tau_{P301L} mutant transgenes into a germline of $PS1_{M146V}$ knockin mouse embryos (Oddo et al. 2003a). The model hinges on the amyloid precursor protein (APP_{Swe}), which leads to the production of Aβ in the brain, and the tau_{P301L} gene, leading to hyperphosphorylation of tau proteins developing into neurofibrillary tangles. In addition, the presenilin 1 mouse gene ($PS1_{M146V}$) interacts with APP_{Swe}, accelerating Aβ accumulation in the brain (Oddo et al. 2003a, b). The 3×Tg-AD mice show an increase in the number of Aβ plaques from three to twelve months of age, and in neurofibrillary tangles from six months of age (Oddo et al. 2008). Sex differences have been found in the development of Aβ pathology in 3×Tg-AD mice. Female 3×Tg-AD mice show increased numbers of Aβ plaques and more behavioural deficits than males. This difference has been attributed to the organizational effects

of neonatal sex hormones (Carroll et al. 2010). Increased β-secretase levels seen in female mice are associated with increased Aβ production and decreased neprilysin levels. Both of these changes are thought to lead to a decrease in the degeneration of Aβ (Hirata-Fukae et al. 2008). The presence of these pathologies, however, cannot predict age-related changes in behaviour in 3×Tg-AD mice (Knight et al. 2013).

A number of studies have reported differences in motor skills between transgenic Alzheimer model mice and their wildtype controls. However, the results of such studies appear contradictory. Deficits in motor performance increase with age in both the $APP_{751}/PS1_{KI}$ (double transgenic) and 5×FAD mouse models of Alzheimer's disease, and are attributed to axonopathy due to increased Aβ deposits (Jawhar et al. 2012). In contrast, compared to controls a tau_{JNPL3} mouse model showed increased Rotarod performance as well as better performance in the balance beam and coat hanger tests (motor performance) compared to controls and this was attributed to the presence of mutant tau protein (Morgan et al. 2008). Finally, the 3×Tg-AD mice were found to outperform controls on the Rotarod test and swam faster than controls in the Morris Water Maze (Filali et al. 2012, Stover 2012). Other studies use mice with similar (tau_{P301S}) or the same (tau_{P301L}) tau mutation as that in the 3×Tg-AD model and have found motor deficits (Scattoni et al. 2010, Xu et al. 2010). The differences in results in motor performance may be due to inherent differences in background strains of the transgenic mice (Brooks et al. 2004, McFadyen et al. 2003).

The accelerating Rotarod assesses motor ability and motor learning of rodents (LeMarec & Lalonde 1997, Hamm et al. 1994, Bohlen et al. 2009). Mice are placed onto a rotating rod and the latency to fall (the time from the beginning of the rod's rotation to when a mouse falls) is recorded. The Rotarod is considered a valid measure of motor ability and learning over short-term (trials) and long-term (days) test durations (Buitrago et al. 2004). This test is powerful because it can be used to detect motor behaviour abnormalities in genetically altered, brain damaged, or drug-treated mice (Rustay et al. 2003; Shiotsuki et al. 2010). However, differences in body weight can confound the measurements of mice tested on the Rotarod (Brown et al. 2002). Mice with lower body weights often outperform heavier mice and, since female mice weigh less than males (Stover 2012), it is important to control for body weight in the Rotarod test.

The present experiment used the accelerating Rotarod to investigate age related changes in motor ability and motor learning of male and female 3×Tg-AD and control (B6129SF1/J) mice from 2 to 15 months of age, in a cross-sectional design. It was hypothesized that (1) the latency to fall for all mice would increase over trials as they learned to stay on the Rotarod (Hamm et al. 1994) and (2) mice with higher body weights would have shorter latencies to fall than those with lower body weights (Brown et al. 2002). Increases in Aβ pathology in female 3×Tg-AD mice suggest that (3) males would outperform females (Carroll et al. 2010). Based on recent literature (Stover 2012, Morgan et al. 2008), it is hypothesized that (4) transgenic mice will have a longer latency to fall than controls.

METHODS

Subjects

Control (B6129SF1/J) and 3×Tg-AD mice were purchased from Jackson Laboratories (Bar Harbor, Maine) and bred at Dalhousie University. This experiment was approved by the Dalhousie University Committee on Laboratory Animals. Mice were weaned at 21 days of age and housed in same-sex groups of two to four in clear plastic cages measuring 28 × 18.75 × 12.5 cm containing woodchip bedding. *Ad libitum* access to Purina rodent chow and water was provided for all mice. Each cage included a PVC enrichment tube (4 cm diameter × 7 cm length). The colony room was kept at 22±2 °C, with a reversed light-dark cycle (lights off from 09:30-21:30). Table 1 shows the distribution of mice tested by genotype, sex, and age. Table 2 gives details of mean body weights of the mice.

Apparatus

The accelerating Rotarod (AccuScan Instruments, Columbus, Ohio), consisted of an acrylic, horizontally-grooved rod (30 mm diameter), rotating about its long axis (Fig 1). The rod was divided into four 11 cm compartments by Plexiglas dividers (30 cm diameter), so that four mice could be tested simultaneously. Below each rod segment was a holding compartment connected to a timer that automatically recorded the latency of each mouse to fall. The Rotarod accelerated from 0.0 to 48.0 rpm over 360 seconds. The testing room (1.12 × 2.60 m) was illuminated by a 60W red light bulb. The experiment followed

Table 1 **Number of female (F) and male (M) 3×Tg-AD and wildtype control mice tested at each age.**

Age	3×Tg-AD	Control	Total
2-month	10F, 8M	8F, 8M	34
6-month	5F, 7M	5F, 6M	23
9-month	9F, 4M	8F, 10M	31
12-month	8F, 5M	10F, 12M	35
15-month	10F, 3M	10F, 11M	34
Total	69	88	157

Table 2 **Mean body weights (g) of mice by age, genotype, and sex, abbreviated.**

Age	3xTg-AD		Control	
	Female	Male	Female	Male
2-month old	18.9	24.2	21.0	26.5
6-month old	27.4	30.8	24.9	32.3
9-month old	33.3	33.1	29.8	33.4
12-month old	36.3	32.9	29.3	38.9
15-month old	38.0	30.8	30.3	40.5

a between-subjects design (genotype × sex × age), with experimenters blind to age and genotype.

Procedure

Mice were tested on the Rotarod for six trials per day for five consecutive days during the dark phase of the light-dark cycle. Mice were weighed daily before being tested. A trial began by placing each mouse onto the stationary rod, with its head facing opposite to the direction of rotation. The Rotarod was switched on and the latency to fall (sec) was displayed on a digital panel and recorded for each mouse. Mice were left in the compartments below the Rotarod until all mice had fallen. The next trial began 60 seconds after the fourth mouse fell. After six trials, the mice were returned to their home cages. If any mouse failed to fall for the entire 360-second trial, it was taken from the rod and placed in its holding compartment, and the latency to fall was recorded as 360 seconds. After each group of mice was tested, the Rotarod was cleaned with a damp paper towel and a drop of dishwashing liquid to remove residual odours.

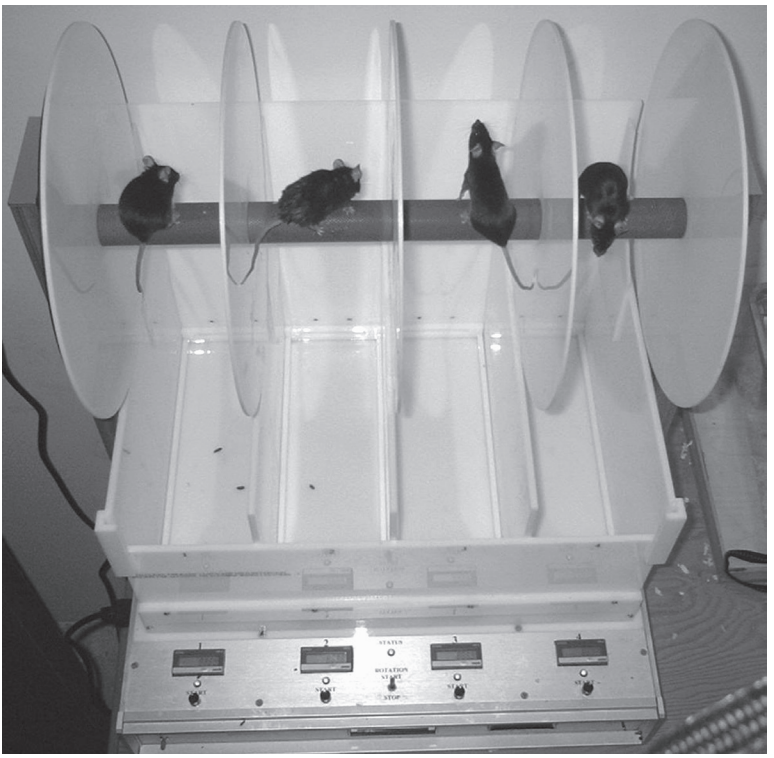

Fig 1 **The Rotarod apparatus, showing four mice being tested, the circular dividers between compartments, the holding compartments, and timers for recording latency to fall.**

Data Analysis

Mean latencies to fall for each mouse were calculated for each test day using Microsoft Excel 2011. An "Improvement score" $\left(\frac{Day\ 5\ Performance - Day\ 1\ Performance}{Day\ 1\ Performance} * 100\right)$ was also computed for each mouse. All statistical analyses were conducted using SPSS 21.0. Correlations were performed between weight and performance on day 5. Repeated measures ANOVAs were performed with mean fall latencies for each day as the within-subjects variable, and genotype, sex, and age as between-subjects variables. Mauchly's (1940) test was performed, and the assumption of sphericity was found to be violated for the model. A second analysis of variance was conducted using the Greenhouse-Geisser model (Girden 1992), and the significance of the F-values computed using this model did not differ from those calculated using the unmodified ANOVA. Therefore the results of the

unmodified ANOVA without corrected degrees of freedom are reported. The improvement scores were assessed using a factorial, genotype by sex by age, ANOVA. Post-hoc t-tests were used to examine differences between groups on each test day. Data was considered significant for $p<0.05$.

RESULTS

No significant correlation was found between body weight and Rotarod performance on day 5 ($r=-0.151$; $df=155$; $p=0.058$), thus weight was not used as a covariate in subsequent analyses. Performance for all mice increased significantly over the five days of testing ($F(4,548)=261.47$, $p<0.001$) (Fig 2A-F). A main effect was found for genotype ($F(1,137)=60.54$, $p<0.001$) as transgenic mice outperformed controls in latency to fall. There was also a main effect of sex ($F(1,137)=4.49$, $p<0.05$) as females outperformed males. No significant main effect was found for age. There was a significant genotype by day interaction ($F(4,548)=26.89$, $p<0.001$) (Fig 2F) as latency to fall increased more rapidly for transgenic mice than control mice over days. No significant sex by day or age by day interactions were found. The interaction between genotype and age was significant ($F(4,137)=3.64$, $p<0.01$). As shown in Figure 2 (A-E), the mean latency to fall of transgenic mice peaked at 6 months of age and decreased as age increased, with the 15 month old group having the lowest latencies. The mean latencies were lower in controls than in transgenic mice at each age, with peaks occurring among controls at 2 and 9 months of age. There was also a significant genotype by age by day interaction ($F(16,548)=2.41$, $p<0.01$). This three-way interaction reflects the finding that the genotype by day interaction was not significant at 2 months of age ($F(4,128)=0.928$, $p=0.45$) but was significant at all other ages: at 6 months ($p<0.001$); at 9 months ($p<0.001$); at 12 months ($p<0.001$); and at 15 months ($p<0.01$) (Fig 2A-E). Post-hoc t-tests indicate the significant differences between genotypes on each test day at each age (Fig 2 A-E). Improvement scores were significantly higher in transgenic mice than in controls ($F(1,137)=15.58$, $p<0.001$) (Fig 3A); and higher in males than females ($F(1,137)=8.08$, $p=0.005$) (Fig 3B). Improvement scores were not significantly affected by age nor were any interactions found.

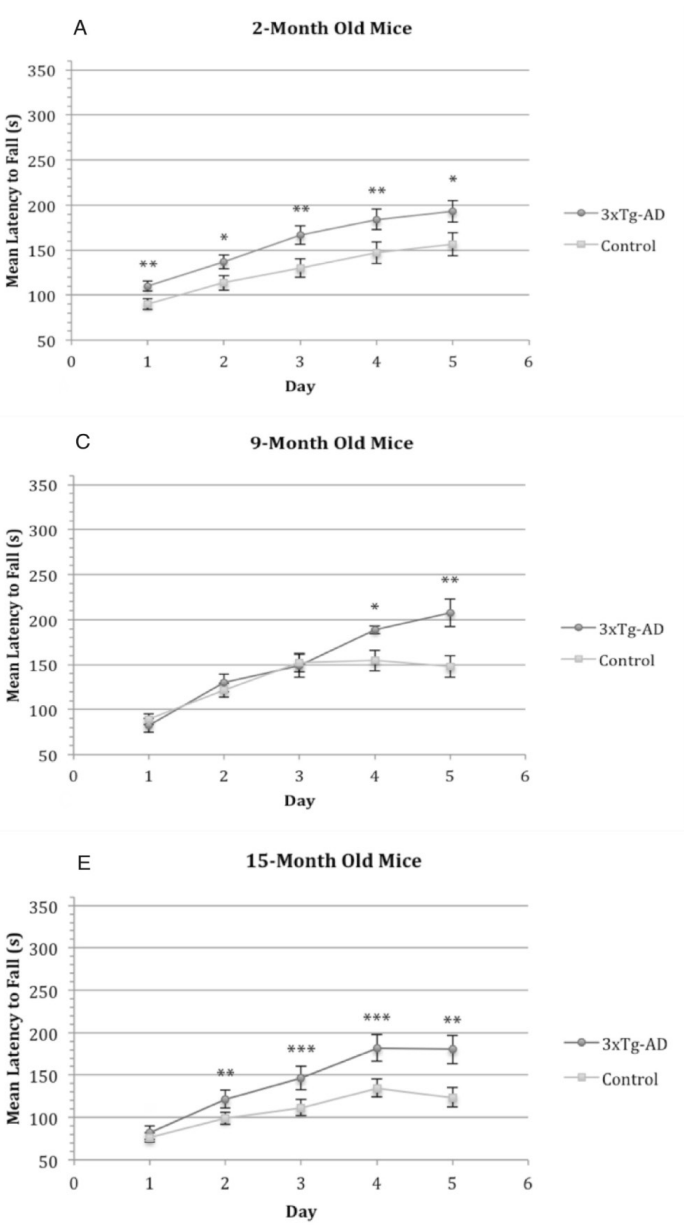

Fig 2 **Mean (±SEM) latency (s) to fall over the 5 days of testing for 3×Tg-AD and control mice at (A) 2 months of age; (B) 6 months of age; (C) 9 months of age; (D) 12 months of age; (E) 15 months of age; and (F) at all ages. Asterisks indicate the level of significance between means for 3×Tg-AD and control mice for each day, at each age (*=p<0.05, **=p<0.01, ***=p<0.001).**

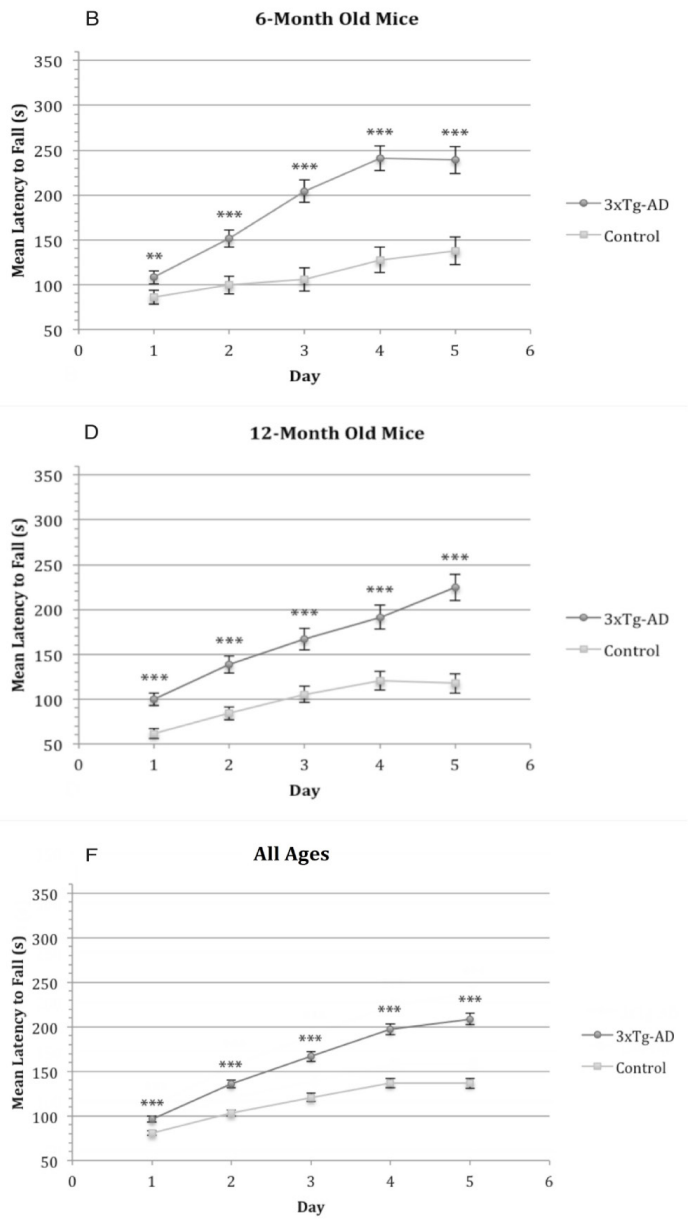
B
6-Month Old Mice
Mean Latency to Fall (s)
Day
3xTg-AD
Control
D
12-Month Old Mice
Mean Latency to Fall (s)
Day
3xTg-AD
Control
F
All Ages
Mean Latency to Fall (s)
Day
3xTg-AD
Control

Fig 2 ***Cont'd***

DISCUSSION

The purpose of this study was to characterize age-related changes in the motor ability and motor learning of male and female 3×Tg-AD mice on the accelerating Rotarod. As hypothesized, (1) the latency to fall for mice significantly increased over the five days of testing at all ages. This indicated that all of the mice tested showed motor learning on the accelerating Rotarod. We hypothesized that (2) lighter mice would outperform heavier mice (Brown et al. 2002), but the results did not indicate any influence of body weight. Increases in Aβ pathology of female 3×Tg-AD mice led to the hypothesis that (3) males would outperform females on the Rotarod (Carroll et al. 2010). This hypothesis was not supported; females had significantly longer latencies than males. This could be in part because female mice tend to have lower body weights than males (Stover 2012), and lower body weights are associated with longer latencies (Brown et al. 2002). However, the improvement scores were significantly higher for males than for females (Fig 3B). Thus, females performed better than males, but males learned more quickly, possibly due to less accumulation of Aβ pathology (Hirata-Fukae et al. 2008). While no main effect was found for age, there was a significant genotype by age interaction. A notable shift occurred at 6 months of age (Fig 2B), where the learning trajectory becomes much steeper in transgenic mice than in controls. This coincides with detectable pathologies in 3×Tg-AD mice (Oddo et al. 2003b). Perhaps unknown neural changes within 3×Tg-AD mice promote motor learning while leading to cognitive and memory impairments (Morgan et al. 2008).

Recent studies on Rotarod performance for 3×Tg-AD mice (Filali et al. 2012, Morgan et al. 2008, Stover 2012) led to the hypothesis that (4) transgenic mice would outperform controls in motor ability and motor learning. Our results supported this hypothesis: transgenic mice had a longer latency to fall and exhibited a greater increase in performance over the five-day test period than controls (Fig 2F). As expected, the improvement score was also significantly higher in transgenic mice than in controls (Fig 3A). Morgan et al. (2008) attributed increases in Rotarod performance to the tau protein. In their study, the Rotarod was the only task that they found to be sensitive enough to detect improvements in transgenic mice with only Aβ pathology over controls. However, Morgan et al. (2008) did not suggest any explanation for the effect of mutant tau. Filali et al. (2012) also noted a significant increase

in Rotarod performance in 3×Tg-AD mice and stated that this result was paradoxical. Similarly, they did not explain their finding. Indeed, this is paradoxical since many tau models display worse performance on the Rotarod than controls (Scattoni et al. 2010, Xu et al. 2010). Harada et al. (1994) found tau proteins to be integral in the organization and stabilization of axonal microtubules in mice. Both microtubules and Aβ, when functioning correctly, are involved in cellular transport (Harada et al. 1994, Igbavboa et al. 2009). Despite that these are both mutant forms, which lead to the overproduction and accumulation of Aβ and tau protein, perhaps together they may promote an ideal transport gradient resulting in the motor improvements seen in 3×Tg-AD mice. While this is conjecture, it may be useful in the future to examine the motor control processes regulated by tau and Aβ proteins.

Mice may need an initial adjustment period to the Rotarod, regardless of genotype or sex. One limitation of a cross-sectional study is that this adjustment period is seen at all ages. In the future, it would be useful

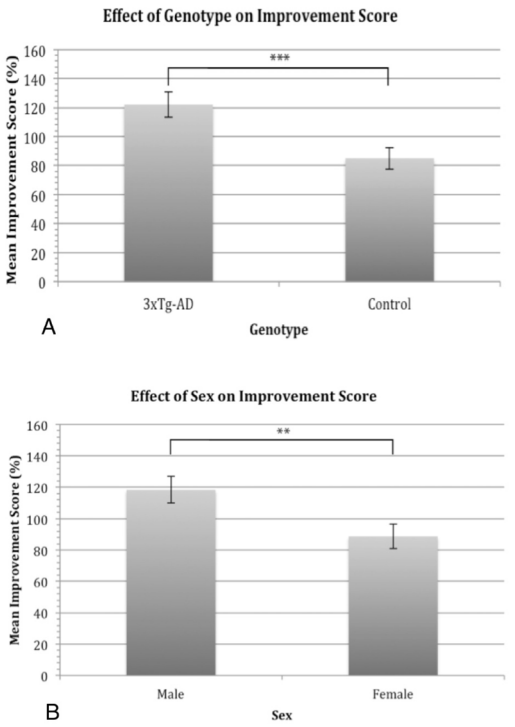

Fig 3 **Mean (±SEM) improvement score (%) showing differences between (A) genotype and (B) sex. (*=p<0.05, **=p<0.01, ***=p<0.001).**

to conduct more experiments longitudinally to look at motor behaviour in mice with extensive experience. Interestingly, Stover (2012) investigated how different starting ages progress longitudinally on the Rotarod (i.e. testing mice for the first time at 9-months and retesting the same mice at older ages) and found the same differences between 3×Tg-AD mice and controls as were found in this study (unpublished results, personal communication, 2013). Another limitation was that the mice were only tested until 15 months of age, though neuropathology in 3×Tg-AD mice exists at older ages (Oddo et al. 2003b). The 15 month 3×Tg-AD mice may not have enough neural loss to detect differences from younger ages. From 18 to 24 months of age, cognitive deficits increase, learning decreases, and the abundance of neuropathologies increase in 3×Tg-AD mice (Billings et al. 2007). Testing older mice, and testing more often throughout the life span, could increase the range of results and better reveal the trajectory of age effects.

There are differences in motor behaviour and motor learning in mice used as background strains for transgenic models (Brooks et al. 2004, McFadyen et al. 2003). The 3×Tg-AD background strain (B6129SF1/J) was used as a control. This strain is considered an appropriate control for the 3×Tg-AD mice. However, the choice of a control is crucial. Even sub-strains display varying behaviour (Stover 2012). Testing multiple sub-strains of the controls against 3×Tg-AD mice could aid in future comparisons. To characterize 3×Tg-AD mice, it would be useful to look at other motor behaviours that occur during Rotarod trials such as gait, foot slips, or Rotarod strategies, such as thigmotaxis, backward walking, and rearing against the dividers. Such observations could help to develop better motor profiles of 3×Tg-AD and control mice. Gait differences between mice (stride length and front paw stride synchrony) have been detected on the Rotarod (Stroombants et al. 2012). Buitrago et al. (2004) suggest that gait differences resulted in varying levels of improvement on the Rotarod. Looking at behavioural strategies or gait may help explain the superior performance seen in 3×Tg-AD mice, which may be linked to specific components of motor behaviour.

In summary, the results of this study suggest that the neuro-genetic mechanisms underlying motor behaviour with the 3×Tg-AD model may provide a link between motor ability and learning impairment in Alzheimer's disease, and provide some insight into the mechanism underlying the relationship between motor learning, sex and age. Gaining a better understanding of motor differences in relation to the

age- and sex-related development of brain pathologies will help to focus future research on this important issue.

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